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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JOHN H. PAUL, MIKE GRAY, and ERICA CASPER

Appeal 2008-002361
Application 10/707,747
Technology Center 1600

Decided:[1] July 31, 2009

Before TONI R. SCHEINER, LORA M. GREEN, and
RICHARD M. LEBOVITZ,
Administrative Patent Judges.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 16-21 and 24-30.[2] We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

The dinoflagellate *Karinia brevis* is the causative agent of recurring toxic red tide blooms in the Gulf of Mexico and off the southeastern Atlantic coast of the United States. Exposure to the toxins produced by *K. brevis* can result in massive fish kills and marine mammal mortality, as well as respiratory distress and food poisoning in humans (Spec. ¶ 5).

Fucoxanthin-containing dinoflagellates like *K. brevis*, and the closely related *K. mikimotoi*, "have a form ID *rbcL* enzyme, and genetic evidence suggests they contain plastids of haptophyte [i.e., primitive algal] origin acquired through tertiary endosymbiosis" (Spec. ¶ 89).

The present invention is directed to a method of detecting *K. brevis* in a sample by amplifying and identifying a gene sequence unique to the *rbcL* (ribulose 1,5-bisphosphate carboxylase-oxygenase large subunit) gene of *K. brevis* (*id.* at ¶ 7).

Claim 16 is representative of the subject matter on appeal:

16. A method for screening a sample for the presence of *K. brevis*, comprising:

subjecting the sample to amplification using a pair of oligonucleotide primers capable of amplifying a target region of the ribulose 1, 5-bi[s]phosphate carboxylase-oxygenase large subunit (rbcL) of *K. brevis*; and

assaying the mRNA for the presence of the amplified target region of the ribulose 1, 5-bi[s]phosphate carboxylase-oxygenase large subunit (rbcL) unique to *K. brevis*.

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[2] Claims 31-36 are pending but have been withdrawn from consideration; claims 1-15, 22, and 23 have been canceled (App. Br. 5).

The Examiner relies on the following evidence:

Gionata Leone et al., *Molecular beacon probes combined with amplification by NASBA enable homogeneous, real-time detection of RNA*, 26 NUCLEIC ACIDS RESEARCH 2150-2155 (1998).

G.A. Buck et al., *Design Strategies and Performance of Custom DNA Sequencing Primers*, 27 BIOTECHNIQUES 528-536 (1999).

Vincent L. Wilson et al., *Species-specific detection of hydrocarbon-utilizing bacteria*, 39 JOURNAL OF MICROBIOLOGICAL METHODS 59-78 (1999).

Holly A. Bowers et al., *Development of Real-Time PCR Assays for Rapid Detection of Pfiesteria piscicida and Related Dinoflagellates*, 66 APPLIED AND ENVIRONMENTAL MICROBIOLOGY 4641-4648 (2000).

Hwan Su Yoon et al., *A single origin of the peridinin- and fucoxanthin-containing plastids in dinoflagellates through tertiary endosymbiosis*, 99 PNAS 11724-11729 (2002).

H.S. Yoon et al., *Karenia brevis ribulose-1,5-bisphosphate carboxylase/ oxygenase (rbcL) gene, partial cds, chloroplast gene for chloroplast product*, GenBank Accession No. AY119786 (2002), available at http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=nuccore&id=21913674

BLAST (Basic Local Alignment Search Tool) search performed at http://www.ncbi.nlm.nih.gov/BLAST/Blast.cgi on December 29, 2006, using a 158-bp query sequence.

Appellants rely on the following additional evidence:

Supporting information for Yoon et al., 99 PNAS 11724-11729 (2002): Table 1. Sample information and GenBank accession numbers for taxa included in phylogenetic analyses (Appellants' Exhibit B), available at http://www.pnas.org/cgi/content/full/172234799/DC1/1

Supporting information for Yoon et al., 99 PNAS 11724-11729 (2002): Table 2. Primers used to amplify the plastid genes (Appellants' Exhibit C), available at http://www.pnas.org/cgi/content/full/172234799/DC1/2

Center for Culture of Marine Phytoplankton Catalog, CCMP718 *Karenia brevis*, (Appellants' Exhibit E), available at http://ccmp.bigelow.org/SD/display.php?strain=CCMP718&genus=Karenia&Species=brevis&Class=Dinophyceae

The Examiner rejected the claims as follows:

- Claims 16-18 under 35 U.S.C. § 103(a) as unpatentable over Yoon, Buck, and GenBank Accession No. AY119786.

- Claims 19-21, 24, and 25 under 35 U.S.C. § 103(a) as unpatentable over Yoon, Bowers, Wilson, Buck, and GenBank Accession No. AY119786.

- Claims 26-30 under 35 U.S.C. § 103(a) as unpatentable over Yoon, Leone, Wilson, Buck, and GenBank Accession No. AY119786.

We reverse.

PRINCIPLES OF LAW

The initial burden of establishing unpatentability rests on the Examiner. *In re Oetiker*, 977 F.2d 1443, 1446 (Fed. Cir. 1992). Nevertheless, there are exceptions where the record justifies shifting the burden to appellant to show a difference between the claimed invention and the prior art. As explained in *In re Best*, 562 F.2d 1252, 1254-1255 (CCPA 1977):

> [W]here the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.

"Whether the rejection is based on 'inherency' under 35 U.S.C. § 102, on 'prima facie obviousness under 35 U.S.C. § 103, jointly or alternatively,

the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products." *Id.* at 1255. "[W]hen the PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990).

"It is a general rule that merely discovering and claiming a new benefit of an *old* process cannot render the process again patentable." *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990). "[A] limitation or the entire invention is inherent and in the public domain if it is the 'natural result flowing from' the explicit disclosure of the prior art." *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1377 (Fed. Cir. 2005) (citations omitted). Thus, "[w]hen considering a prior art method, the anticipation doctrine examines the natural and inherent results in that method without regard to the full recognition of those benefits or characteristics within the art field at the time of the prior art disclosure." *Id.* at 1378.

THE ISSUES

There are three obviousness rejections of the claims. Each of the three rejections is based, at least in part, on two alternative rationales:

(1) The Examiner finds that Yoon's *rbcL* primers "amplify a region unique to *K. brevis*" (Ans. 5), "[t]herefore, Yoon teaches species-specific detection of *K. brevis*" (*id.* at 19). Appellants contend that "Yoon does not teach the use of species specific primers. . . . Rather, Yoon used primers specific to the plastids being tested (namely, the *psa*A, *psa*B and *rbc*L genes) and not a particular species" (App. Br. 10). Appellants contend that

"the method employed by Yoon is not capable of detecting *K. brevis* in a sample because numerous species would provide false positives" (*id.* at 12).

The threshold issue raised by this basis of the Examiner's rejection is whether the evidence relied on by the Examiner is sufficient to justify shifting the burden to Appellants to establish that Yoon's primers would not amplify or could not be used to assay a region unique to *K. brevis*. If so, the succeeding issue is whether Appellants have met their burden.

(2) On the other hand, the Examiner finds that "the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoon" (Ans. 7), and concludes that the claimed primers would have been "*prima facie* obvious over the cited references in the absence of secondary considerations" (*id.*).

Appellants contend that "[n]othing in Yoon teaches that the rbcL gene of *K. brevis* contains a sequence that is unique to that species" (App. Br. 10), and there is "no teaching of what portion, if any, of the sequence deposited in the GenBank database is unique to *K. brevis*" (*id.* at 13), "or that the rbcL gene is a likely candidate for containing a unique sequence" (*id.*).

The issue raised by this alternate basis of the rejection is whether Appellants have shown that the Examiner erred in concluding that primers capable of amplifying a region of the *rbcL* gene unique to *K. brevis* would have been obvious over the oligonucleotides disclosed by Yoon.

FINDINGS OF FACT

FF1 Claim 16 is directed to a method of screening a sample for the presence of the dinoflagellate *Karenia brevis*, comprising subjecting the sample to amplification using a pair of oligonucleotide primers capable of amplifying a target region of the *rbcL* gene of *K. brevis*, and assaying the amplified sample for the presence of an amplified target region of the *rcbL* gene unique to *K. brevis*.

FF2 Figure 2 of the Specification is a neighbor-joining phylogenetic tree showing relationships between *rbcL* sequences from *K. brevis* and other phytoplankton species, as well as "clones [of *K. brevis*] obtained . . . [from] the Gulf of Mexico" (Spec. ¶ 12).

FF3 "Sequence data from the *K. brevis rbcL* clones show a short (91-bp) region that is markedly different from *K[arenia] mikimotoi's rbcL* sequence" (Spec. ¶ 97).

FF4 Appellants selected that "markedly different" region of the *rbcL* gene of *K. brevis* "as the target for a primer and probe set for the Taq-Man *Taq* nuclease assay. A primer set [SEQ ID NOS: 1 and 2] and an internal fluoroprobe [SEQ ID NO: 3] were designed to amplify and detect the 91-bp region" (Spec. ¶ 97).

FF5 "All nontarget strains, their representative accession numbers, and their relationships based on deduced amino acid residues are shown in FIG. 2" (Spec. ¶ 96). "Boldface taxa [in Figure 2] were tested by real-time PCR as nontarget controls" and "[t]here were many taxa tested as nontarget strains whose *rbcL* sequences were not available in GenBank" (*id.* at ¶ 12).

FF6 According to Appellants, "[t]he Taq-Man probe-based RT-PCR assay (91-bp amplicon) yields only positive results with *K. brevis* strains

(FIG. 2). All other dinoflagellates (including *K. mikimotoi*) and algal strains resulted in no amplification" even though "[a]ll strains tested were present in sufficient concentrations to allow for amplification based on the lowest detectable concentration of *K. brevis*" (Spec. ¶ 100).

FF7 Yoon sequenced the plastid-encoded *psa*A, *psa*B, and "Form 1" *rbcL* genes from pure cultures of various red and dinoflagellate algae to determine whether the fucoxanthin-containing plastids "found in taxa such as *Karlodinium micrum* and *Karenia* spp. . . . originated from a haptophyte [i.e., primitive algae] tertiary endosymbiosis in an ancestral peridinin-containing dinoflagellate" (Yoon 11724, col. 1).

FF8 Yoon's *rbcL* primers are listed in Appellants' Exhibit C by name and sequence - all are described as "general" with the exception of one primer said to be specific to *Bangiaceae*.

FF9 Yoon concludes that the two genera of fucoxanthin-containing dinoflagellates tested, *Karenia* and *Karlodinium*, "are paraphyletic at the base of the haptophyte clade" based, in part, on analysis of their *rbcL* genes (Yoon, ¶ bridging pp. 11725 and 11726). That is, Yoon concludes that *Karenia* and *Karlodinium* each contain some, but not all, of the descendants of a single common haptophyte ancestor, and that the Form I *rbcL* gene was acquired early in the lineage of these related organisms, and is "the primitive (not derived . . .) condition in dinoflagellates" (*id.* at 11724, col. 1).

FF10 Thus, there is no indication in Yoon that there is any difference between the *rbcL* genes from *Karenia* spp. and *Karlodinium*.

FF11 A BLAST search performed by the Examiner on December 29, 2006, using a 158-bp query sequence, identified one sequence identical to the query sequence, and eight other sequences with significant alignments to

the query, all of them attributed to the *rbcL* genes of various isolates of *K. brevis*. *See* the listing of evidence relied on by the Examiner above.

FF12 The Examiner asserts that the results of the BLAST search "indicate[ ] [Yoon's] primers amplify a region unique to *K. brevis* and not other *Karenia* species such as *K. mikimotoi*" (Ans. 6), but does not explain how the 158-bp query sequence used in the BLAST search was chosen, or what, if any, relationship exists between the query sequence and any of Yoon's primers.

Analysis

Appellants contend that Yoon "teaches a method of determining the origin of plastids in red algae and dinoflagellates" (App. Br. 9), and "at best, teaches a method of amplifying a pure sample rather than detecting the presence of *K. brevis* in an impure sample" (*id.*). Appellants contend that "Yoon does not teach the use of species specific primers. . . . Rather, Yoon used primers specific to the plastids being tested (namely, the *psa*A, *psa*B and *rbc*L genes) and not a particular species" (*id.* at 10). Appellants argue that "the references do not teach or infer that a unique sequence exists on the rbcL gene" of *K. brevis* (*id.* at 13). On the contrary, Appellants contend that Yoon describes the Form I *rbcL* gene as "the primitive (i.e., not derived) condition in dinoflagellates, emphasizing its ubiquitous nature" (*id.*). Thus, Appellants contend, there is "no teaching of what portion, if any, of the sequence deposited in the GenBank Database is unique to *K. brevis*" (*id.* at 13).

It is true that Yoon does not disclose whether any of the primers used to amplify sequences from the *rbcL* gene in the *K. brevis* sample amplify a region of the gene unique to *K. brevis* (FF9, FF10). It is also true that Yoon

amplifies the *rbcL* gene in a *K. brevis* culture, rather than a sample of mixed or unknown composition (FF7). However, if one or more of Yoon's primers actually amplified a region of *rbcL* unique to *K. brevis*, the fact that Yoon describes the primers as general, rather than species-specific (FF8), would be irrelevant. The species-specificity of Yoon's primers need not be recognized as long as amplifying a region of the *rbcL* gene unique to *K. brevis* is the "natural result flowing from" Yoon's method. *See e.g., Woodruff*, 919 F.2d at 1578, and *Perricone*, 432 F.3d at 1377. The fact that Yoon amplified a portion of the *rbcL* gene in a *K. brevis* culture, rather than an impure sample, would be equally irrelevant, as the claims do not require an impure sample.

Nevertheless, as discussed above, the threshold issue raised by this first aspect of the Examiner's rejection is whether the evidence of record is sufficient to justify shifting the burden to Appellants to disprove the Examiner's assertion that Yoon's primers would amplify a region of the *rcbL* gene of *K. brevis*, and no other dinoflagellates or algae. We agree with Appellants that the result of the Examiner's BLAST search with a 158-basepair sequence of the *K. brevis rbcL* gene does not represent a sound or adequate basis to shift the burden of proof to Appellants. *See Best*, 562 F.2d at 1255; *Spada*, 911 F.2d at 708. The present Specification indicates that the *rbcL* sequences of "many taxa tested as nontarget strains . . . were not available in GenBank" (FF5), but even if we assume for the sake of argument that the sequences of other related organisms *were* available in GenBank for comparison with the query sequence, the Examiner has not explained the relationship between the BLAST query and Yoon's primers. Therefore, the Examiner has not provided evidence, or any "sound basis for

believing", that the Yoon's primers amplified or assayed mRNA for an *rbcL* region which is "unique to *K. brevis*" as required by the claims.

In an alternative rationale, the Examiner finds that "the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoon, which are 100% derived from sequences expressly suggested by the prior art of Yoon" (Ans. 7), and concludes that "a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, [thus] the claimed primers are *prima facie* obvious over the cited references" (*id.*). The Examiner further concludes that "should the primers taught by Yoon detect . . . [a] sequence in a related species such a *K. mikimotoi*, it would have been prima facie obvious . . . to design other species-specific primers within the 158-bp sequence for the purposes of screening samples for specific detection of K. brevis" (*id.* at 20).

Appellants contend that "the references do not teach or infer that a unique sequence exists on the rbcL gene" (App. Br. 13). That is, "[n]othing in Yoon teaches that the rbcL gene of *K. brevis* contains a sequence that is unique to that species" (*id.* at 10). In addition, Appellants contend that the listing for GenBank Accession No. AY119786 represents "less than two-thirds of *Karenia's* rbcL gene" and there is "no teaching of what portion, if any, of the sequence deposited in the GenBank Database is unique to *K. brevis*, or of any method to determine same" (*id.* at 13).

Appellants' argument is persuasive. Appellants identified a 91 bp region of the *rbcL* gene of *K. brevis* that is unique to *K. brevis*, and disclosed forward and reverse primers (SEQ ID NOS: 1 and 2) to amplify that region, as well as an internal probe (SEQ ID NO: 3) to detect the amplified region. The Examiner has not explained how or why the primers used in the claimed

method, or any other primers that would amplify or could be used to assay a region of the *rbcL* gene unique to *K. brevis*, "simply represent structural homologs" of Yoon's primers. Nor has the Examiner established that "structural analogs" of Yoon's primers, assuming one of skill in the art would have had reason to make them, would be capable of amplifying a region of the *rbcL* gene unique to *K. brevis*.

Moreover, the Examiner's assertion that it would have been obvious to design "species-specific primers . . . for the purposes of screening samples for specific detection of K. brevis" (Ans. 20), "should the primers taught by Yoon detect . . . [a] sequence in a related species such a *K. mikimotoi*" (*id.*) presupposes that one of skill in the art would have expected *K. brevis* to have an *rbcL* gene with a unique sequence. However, the Examiner has not identified anything in the prior art to suggest anything of the kind. Rather, Yoon emphasizes that paraphyletic dinoflagellates like *Karenia brevis*, *Karenia mikimotoi*, and *Karlodinium* obtained the *rbcL* gene before the split in their lineages, and it persists in the primitive condition (FF7, FF9, FF10).

CONCLUSIONS OF LAW

The evidence relied on by the Examiner is not sufficient to shift the burden to Appellants to establish that Yoon's primers are not capable of amplifying a region unique to *K. brevis*. Moreover, Appellants have established that the Examiner erred in concluding that primers capable of amplifying a region of the *rbcL* gene unique to *K. brevis* would have been obvious over the oligonucleotides disclosed by Yoon.

SUMMARY

- The rejection of claims 16-18 under 35 U.S.C. § 103(a) as unpatentable over Yoon, Buck, and GenBank Accession No. AY119786 is reversed.

- The rejection of claims 19-21, 24, and 25 under 35 U.S.C. § 103(a) as unpatentable over Yoon, Bowers, Wilson, Buck, and GenBank Accession No. AY119786 is reversed.

- The rejection of claims 26-30 under 35 U.S.C. § 103(a) as unpatentable over Yoon, Leone, Wilson, Buck, and GenBank Accession No. AY119786 is reversed.

REVERSED

DM

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